linked with polyalkenyl ether or divinyl glycol, wherein the water-insoluble swellable mucoadhesive polymer is preferably, NOVEON or CARBOMER. The water-insoluble swellable mucoadhesive polymer may be present at a concentration of from 0.1% to 20% by weight.

Please replace the second paragraph of page 6 with:

The invention is also directed to a pharmaceutical gel which when applied to the skin or mucosal surface forms a film, said gel comprising a solvent vehicle, at least one water-insoluble swellable mucoadhesive polymer, at least one pH-sensitive film-forming polymer, and at least one molecule of interest, wherein said film is formed due to changes in pH and desolvation of the polymer, and wherein said film provides for the delivery of the molecule of interest to or through the application site. The solvent vehicle may be comprised of at least 25 to 100 parts water with 0 to 75 parts of ethanol, propylene glycol, glycerin, polyethylene glycol, or combinations thereof. The water-insoluble swellable mucoadhesive polymer may be polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol. Preferably, the water-insoluble swellable mucoadhesive polymer is NOVEON or CARBOMER. The water-insoluble swellable mucoadhesive polymer may be present at a concentration of from 0.1% to 20% by weight.

Please replace the second paragraph of page 7 with:

The water-insoluble swellable mucoadhesive polymer is polyacrylic acid cross-linked with polyalkenyl ether or divinyl glycol. Preferably, the water-insoluble swellable mucoadhesive polymer is NOVEON or CARBOMER. The water-insoluble swellable mucoadhesive polymer may be present in the pH-sensitive mucoadhesive layer at a concentration of from 0.1% to 20% by weight.

Please replace the second-to-last paragraph of page 9 with:

Figure 2 shows an *in vitro* adhesion time of ¼ inch wax-film composites (n=3 each) on glass submerged in 40 mM KH_2PO_4/NaOH buffer, pH 6 at 37°C (unstirred). Each mucoadhesive layer contains 5.0-5.3 mg of total polymer comprised of NOVEON and EUDRAGIT S100 in the ratios indicated. The wax layer consists of DENTSPLY® Utility Wax containing 1% w/w tragacanth polymer. *Indicates that different volumes of mucoadhesive gels were cast as described in Example 8. See Table 1 and Example 8 for additional details.

Please replace the last paragraph of page 9 with:

A10

Figure 3 shows *in vitro* adhesion time of ¼ inch wax-film composites (n=3 each) on glass submerged in 40 mM KH_2PO_4/NaOH buffer, pH 6 at 37°C (stirred at 100 rpms). Each mucoadhesive layer contains from 1.2 mg to 11.2 mg of total polymer comprised of NOVEON and EUDRAGIT S100 in a weight ratio of 3:1. The wax layer consists of DENTSPLY® Utility Wax containing 1% w/w tragacanth polymer. See Table 2 and Example 9 for additional details.

Please replace the third full paragraph of page 10 with:

A11

Figure 6 shows the release of plasmid DNA pre-loaded into wax-film composites. Wax-film composites were made as described in Example 10 using a mucoadhesive gel comprised of NOVEON/EUDRAGIT S100 (3:1 w/w) and plasmid DNA. The wax layer consists of DENTSPLY® Utility Wax containing 1% w/w tragacanth polymer. Five ¼ inch wax-film composites containing of plasmid DNA (5 μg) were submerged separately into 1 mL 10 mM PBS buffer, pH 7.4 at 37°C. At various times, exactly 100 μL solution was aliquoted for DNA quantitation using the PicoGreen DNA Quantitation Kit. Exactly 100 μL fresh PBS was added to replace the removed volume at each time point.

Please replace the fourth full paragraph of page 10 with:

A12

Figure 7 shows the release of plasmid DNA post-loaded into wax-film composites. Wax-film composites were made as described in Example 10 using a mucoadhesive gel comprised of NOVEON/EUDRAGIT S100 (3:1 w/w). The wax layer consists of DENTSPLY® Utility Wax containing 1% w/w tragacanth polymer. Plasmid DNA (5 μg) was added to five individual ¼ inch wax-film composites, allowed to air dry for 4 hours, and then submerged separately into 1 mL 10 mM PBS buffer, pH 7.4 at 37°C. At various times, exactly 100 μL solution was aliquoted for DNA quantitation using the PicoGreen DNA Quantitation Kit. Exactly 100 μL fresh PBS was added to replace the removed volume at each time point.

Please replace the first full paragraph of page 25 with:

A13

A plethora of different mucoadhesive gel formulations have been described in the literature and several are now marketed products. Typically, the mucoadhesive component of

the formulation is a biocompatible polymer, such as polyacrylic acid that is cross-linked with an acceptable agent to create an insoluble gel. The use of an insoluble gel is desirable since it remains in contact with the mucosal tissue for much longer periods of time. Cross-linked polyacrylic acid polymers, such as NOVEON and CARBOMER, have been shown to stay attached to the mucosal lining in the vagina for up to three to five days (March and Nakamura, 1993). Further, gels containing NOVEON and/or CARBOMER have been used as vaginal lubricants so it is envisioned that the described gels may be used during sexual intercourse. NOVEON and CARBOMER-based polymers are weak acids and contain many negatively-charged carboxyl-groups. The multiple negative charges on these polymers promote hydrogen-bonding between the polymers and the negatively charged mucin, the main glycoprotein that allows for the attachment of mucus to the epithelial lining of the vaginal wall (Park and Robinson, 1985). NOVEON and CARBOMER-based polymers have been shown to have maximum hydrogen-bonding in the pH range of 4.0 to 6.0. This is ideal for use in the vagina which has a normal pH value of about 4.5 (Stevens-Simon et al., 1994; Garcia-Closas, et al., 1999). It is envisioned that gels comprised of pH-sensitive polymers and water-insoluble mucoadhesive polymers such as NOVEON and CARBOMER may provide superior delivery of molecules of interest to the vagina since the lower pH of the vagina will cause the pH-sensitive polymer to form a long lasting film to retain and/or deliver the molecule of interest in a more efficacious manner.

A13 cont'd

Please replace the first paragraph of page 26 with:

Materials: Recombinant hirudin and bovine α-thrombin are from Sigma Chemicals (St. Louis, MO). Chromozym-TH is from Boehringer Mannheim. Chitosan Seacure 143 (85-90% deacetylated) is from Natural Biopolymer Inc. (Raymond, WA). All EUDRAGIT polymers were obtained from Rohm America, Inc. (Piscataway, NJ). NOVEON and CARBOMERs were obtained from BF Goodrich (Cleveland, Ohio). Glycerin, polyethylene glycol 400, isopropyl myristate, ethanol, sodium hydroxide, and propylene glycol were all of USP/NF grade and were purchased from Spectrum Quality Products, Inc. (New Brunswick, NJ). PicoGreen dsDNA Quantitation Kit was purchased from Molecular Probes, Inc. (Eugene, OR). DENTSPLY® Utility Wax was obtained from DENTSPLY International (York, PA).

A14

Please replace the second paragraph of page 26 with:

A placebo pH-sensitive mucoadhesive film-forming gel was made as follows. Water (44.1 % w/w) was added to a 250 mL stainless steel beaker and stirring was begun at 200 rpm using a Caframo Stirrer. NOVEON (0.5% w/w) and CARBOMER 971 (0.8% w/w) were added very slowly to the stirring water until the solution was clear and viscous with no visible solid material in solution. Glycerin (50.4% w/w) was then added to the polymers in water. EUDRAGIT L100 (2.0% w/w) was added and the solution and the viscous solution became slightly milky in color and less viscous. 18% sodium hydroxide (2.2% w/w) was then added and the whitish gel became viscous. The pH of the placebo gel was measured by taking 1 mL of the gel and dispersing it into 5 mL water and measuring the pH after 1 hour. The pH of the gel was 6.3 $\pm$ 0.02 (n = 3). When the placebo gel was spread onto the skin of a human volunteer's hand; it produced a clear film. Placebo gel stored under controlled conditions at 25°C/60% Relative Humidity for 1 week and 1 month had pH of 6.2 $\pm$ 0.07 (n = 3) and 6.2 $\pm$ 0.06 (n = 3), respectively. Placebo gel stored under controlled conditions at 40°C/75% Relative Humidity for 1 week and 1 month had pH of 6.1 $\pm$ 0.03 (n = 3) and 6.1 $\pm$ 0.09 (n = 3), respectively. These results demonstrated that the placebo gel was stable when stored under the conditions tested.

II. Response to Office Action

A. Status of the Claims and Specification

Claims 1-32 remain pending. Claims 1, 4, 8, 19, and 23 have been amended. Support for the amendment to claim 1 may be found throughout the specification, and particularly at page 11, last paragraph. The other claim amendments capitalize trademarks. The specification has also been amended to capitalize trademarks.

The substance of all the amendments is illustrated in Appendix A. For the Examiner's convenience, the pending claims, reflecting the amendments made in this response, are attached in Appendix B.